

PHARMACEUTICAL STABILITY OF PROMETHAZINE IN IV INFUSION FLUIDS

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Statement of the Research Problem: There is insufficient data available concerning the stability of promethazine in different intravenous (IV) formulations.

Research Objective: To determine the stability of promethazine in different IV formulations with regard to temperature and light.

H₀: There is no statistically significant difference in the stability of promethazine in different IV formulations with regard to temperature and light.

H_A: There is a statistically significant difference in the stability of promethazine in different IV formulations with regard to temperature and light.

BACKGROUND

Promethazine was first released under the brand name Phenergan by Wyeth Pharmaceuticals in 1956.¹ In many hospitals, it is commonly administered via slow intravenous push (IVP) for the treatment of nausea and vomiting (NV) symptoms in post-operative patients.² Unfortunately, the intravenous (IV) promethazine formulation, given via IVP, has been questioned recently because of the serious complications that may result from improper administration.²

Promethazine injection has been shown to cause severe chemical irritation and damage to tissues.^{1,2,4,7} Irritation and damage can result from perivascular extravasation.¹ According to the University of Illinois at Chicago College of Pharmacy, "Extravasation is defined as the leakage of a drug or solution from a vein into the extravascular space."³ Additional adverse events can result from unintentional intra-arterial injection as well as from intraneuronal or perineuronal infiltration.¹ Adverse event reports related to intra-arterial administration include burning, pain, thrombophlebitis, tissue necrosis, and gangrene.⁴

In 2006, the Institute for Safe Medication Practices (ISMP) proposed that the FDA reexamine promethazine product labeling and consider eliminating the IV route of administration.² Concern was expressed for the frequent incidence of injury, ranging from mild

to severe, resulting from promethazine infiltration or unintended intra-arterial injection.² In 2009, the FDA published a safety alert titled “Information for Healthcare Professionals: Intravenous Promethazine and Severe Tissue Injury, Including Gangrene” in order to inform healthcare professionals of the risks of severe tissue damage associated with promethazine administered via IVP.¹ In the safety alert, the FDA ordered a Boxed Warning for promethazine injection, USP products to clearly convey the risk of severe tissue damage.¹ Furthermore, the FDA revised the maximum recommended concentration for IV administration of promethazine to 25 mg/mL as well as the maximum recommended rate of administration via the IV route to 25 mg/min.¹

Because of promethazine’s potential for adverse effects, alternative drug therapies have been proposed such as ondansetron and prochlorperazine.² Ondansetron and promethazine have similar efficacies in treating NV symptoms; however, ondansetron is preferred over promethazine due to its milder adverse effect profile.⁵ In patients that do not respond to ondansetron, other pharmacologic therapies are required. Prochlorperazine is also effective in treating NV. Unfortunately, its practical use has been limited by shortages.⁶ Such availability issues could make it difficult to include in a hospital formulary.

Another option for treating NV in post-operative patients is administering promethazine via intravenous piggy back (IVPB).² According to the ISMP, diluting promethazine in an IV fluid, such as normal saline, reduces the vesicant effects and enables slow administration of the drug.² Diluting the drug also allows healthcare professionals to recognize extravasation more quickly than if it were given in a smaller volume.² Currently, hospital pharmacists prepare the diluted solutions of promethazine for IVPB administration as needed for individual patients. However, time is often an issue for hospital pharmacists to provide this medication to every patient. Therefore, it would be beneficial for pharmacists to be able to prepare these solutions in

advance. Unfortunately, there is little to no data on the stability of promethazine in IVPB formulations past twenty four hours.

According to the *Handbook on Injectable Drugs*, promethazine is stable in normal saline 0.9% at a concentration of 100 mg/L for twenty four hours at 21°C in the dark.⁷ Furthermore, a study at the Anne Arundel Medical Center successfully used a formulation of 6.25 mg of promethazine in a solution of sterile water and found it to be stable for up to 30 days.⁸ However, determining stability was not the primary objective of the study.

OBJECTIVE

In order to promote administering promethazine via IVPB in hospitals, the stability of promethazine will be determined in different IV formulations. With proper stability information, hospital pharmacists can more efficiently prepare promethazine treatments in advance so that every patient is able to receive their treatment quickly and efficiently thereby reducing adverse effects as seen with administering promethazine via IVP.

PROPOSED MATERIALS AND METHODS

Chemicals and Reagents

For our study, promethazine will be formulated in three IV fluids: normal saline (NS), dextrose 5% in water (D5W), and Lactated Ringer's solution (LR). Promethazine, methanol, and acetic acid will be obtained from Sigma Aldrich (St. Louis, MO). NS, D5W, and LR will be provided by the Pharmacy Department at Greene Memorial Hospital (Xenia, OH).

Stability Studies and Sample Preparation

Promethazine will be prepared at a concentration of 12.5 mg/mL in fifteen separate 50 mL Intravenous Piggyback (IVPB) bags. Five bags will contain NS, another five will contain D5W, and the last five bags will contain LR. All solutions will be prepared in triplicates. One of each type of IVPB solution will be stored at room temperature (21°C), 4°C, and 37°C in the dark. Additionally, one of each type of IVPB solution will be stored under white light and one of each type of IVPB solution will be stored under UV light at room temperature. The samples stored in the dark at room temperature will serve as the control group. Ten microliter (µL) aliquots will be removed from each sample at zero, four, eight, twelve, and twenty-four hours and injected onto the column run at a flow rate of 1.0 mL/min using methanol and acetic acid (100:0.1 volume/volume) as the mobile phase. After the initial twenty-four hours, if no degradation has occurred, we will analyze the sample at twelve-hour intervals until degradation is observed. Promethazine tested at zero hours will be considered our standard. Any deviation from this standard will be considered degradation, and testing will be discontinued.

HPLC Analysis

Dionex® Ultimate 3000 HPLC will be used to analyze the degradation of promethazine. The chromatographic system is equipped with a quaternary analytical pump, an autosampler with integrated column compartment, a diode array detector, and an automated fraction collector. The HPLC is equipped with an Acclaim® 120 C18 guard column (4.6 x 10 mm, 5 µm) and an Acclaim® 120 C18 analytical column (4.6 x 150 mm, 5 µm) as the stationary phase. The mobile phase will consist of methanol and acetic acid (100:0.1 volume/volume). The flow rate will be 1.0 mL/min and, and the injection volume will be 10 µL.

HPLC Calibration

Initial HPLC runs will be conducted to establish the retention time and purity of the promethazine reference standard. Calibration standards of concentration 0, 25, 50, 100, 150, 200, and 250 mg/L will be prepared by diluting a stock solution of promethazine of concentration 1000 mg/L

HPLC Validation

The HPLC method will be validated for precision, accuracy, repeatability, and limit of quantification according to ICH (International Conference on Harmonization) guidelines.¹ The accuracy and the precision of our proposed method will be obtained using analyses of our standard reference material, promethazine. An HPLC analysis will be used to measure the promethazine present in a given sample. Accuracy will be determined by comparing promethazine of known purity to promethazine of known quantity in LR, D5W, and NS. Accuracy will also be assessed on samples with known amounts of impurities. Accuracy will be assessed using a minimum of nine determinations over a minimum of three concentrations. Precision will be investigated through multiple sampling of homogeneous and authentic samples under the prescribed conditions. Repeatability will also be assessed using a minimum of nine determinations (three concentrations/three replicates each). The quantitation limit of this analytical procedure will be determined by the analysis of samples with known concentrations of promethazine and by establishing the minimum level at which promethazine can be quantified with acceptable accuracy and precision.⁹

Data Analysis

Chromeleon® software, Microsoft Excel, and IBM SPSS 22 will be used for data and statistical analyses. Descriptives will be used to determine the length of stability of promethazine in various IV formulations and storage conditions after receiving data from the HPLC analysis. We can then use the descriptives to evaluate the options for optimal storage conditions in healthcare facilities.

TIMELINE

We plan to begin analyzing samples in September of 2015. We will begin by evaluating one bag each of the three promethazine formulations (NS, D5W and LR) at room temperature (21°C) in the dark as a control. Each following month, we intend to analyze each of the formulations in another combination of temperature and light conditions. We plan to finish data collection in February of 2016 and begin data analysis in March of 2016.

LIMITATIONS

This study has several anticipated limitations. One such limitation is our inexperience as researchers. Another limitation is that we are only testing a small amount of sample due to limited available resources. Finally, there was a limited amount of literature accessible to help inform our study.

FUTURE DIRECTIONS

The main intent of our study is to inform healthcare professionals on the optimal use of promethazine formulated in IVPB solutions. Depending on our findings, healthcare facilities

may be able to increase efficiency and decrease costs by reducing waste. Additionally, based on our outcomes, it may be beneficial to expand our research to include additional IV solutions and storage conditions.

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